FMR1 gene

fragile X mental retardation 1

Normal Function

The *FMR1* gene provides instructions for making a protein called FMRP. This protein is present in many tissues, including the brain, testes, and ovaries. In the brain, it may play a role in the development of connections between nerve cells (synapses), where cell-to-cell communication occurs. The synapses can change and adapt over time in response to experience (a characteristic called synaptic plasticity). FMRP may help regulate synaptic plasticity, which is important for learning and memory. The protein's role in the testes and ovaries is not well understood.

Researchers believe that FMRP acts as a shuttle within cells by transporting molecules called messenger RNA (mRNA), which serve as the genetic blueprint for making proteins. FMRP likely carries mRNA molecules from the nucleus to areas of the cell where proteins are assembled. FMRP also helps control when the instructions in these mRNA molecules are used to build proteins, some of which may be important for functioning of the nerves, testes, or ovaries.

One region of the *FMR1* gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (nucleotides) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40. This CGG repeat segment is typically interrupted several times by a different three-base sequence, AGG. Having AGG scattered among the CGG triplets appears to help stabilize the long repeated segment.

Health Conditions Related to Genetic Changes

fragile X syndrome

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the *FMR1* gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the *FMR1* gene is turned off (silenced) and makes very little or no protein. A loss or shortage of FMRP disrupts normal functions of nerve cells and, consequently, the nervous system, causing severe learning problems, intellectual disability, and the other features of fragile X syndrome. About one-third of males with an *FMR1* gene mutation and the characteristic signs of fragile X syndrome also have features of autism spectrum disorders that affect communication and social interaction.

Fewer than 1 percent of all cases of fragile X syndrome are caused by other changes in the *FMR1* gene. Mutations may delete part or all of the gene or change one of the building blocks (amino acids) used to make FMRP. These genetic changes alter the 3-dimensional shape of the protein or prevent any protein from being produced. The abnormal or missing protein disrupts nervous system functions, leading to the signs and symptoms of fragile X syndrome.

fragile X-associated primary ovarian insufficiency

A trinucleotide repeat expansion in the *FMR1* gene increases a woman's risk of developing a condition called fragile X-associated primary ovarian insufficiency (FXPOI). In this condition, the CGG trinucleotide repeat in the *FMR1* gene is repeated about 55 to 200 times, which is referred to as a premutation. Women who develop FXPOI may experience irregular menstrual cycles, an inability to have children (infertility), early menopause, and elevated levels of a hormone known as follicle stimulating hormone (FSH). About 20 percent of women with a premutation have the most serious form of the condition, called overt POI, which leads to abnormal menstrual cycles and elevated FSH levels before age 40 and often causes infertility. Other women with the premutation have occult POI, a milder form of the condition that causes reduced fertility, although the women have normal menstrual cycles.

For unknown reasons, the premutation leads to the overproduction of abnormal *FMR1* mRNA that contains the repeat expansion. Researchers believe that the abnormal mRNA causes the signs and symptoms of FXPOI. It is thought that the mRNA attaches (binds) to other proteins and keeps them from performing their functions. In addition, the repeats make producing protein from the blueprint more difficult, and consequently, some people with the *FMR1* gene premutation have lower than normal amounts of FMRP. As a result, they may have mild versions of the physical features seen in fragile X syndrome (described above), such as prominent ears, and may experience emotional problems such as anxiety or depression.

fragile X-associated tremor/ataxia syndrome

Men, and some women, with an *FMR1* gene premutation are at increased risk of developing a disorder known as fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is characterized by progressive problems with movement (ataxia), tremor, memory loss, reduced sensation in the lower extremities (peripheral neuropathy), and mental and behavioral changes. The disorder usually develops late in life and worsens over time.

As in FXPOI (described above), the premutation causes overproduction of abnormal *FMR1* mRNA containing the expanded repeat region, and researchers believe that this abnormal mRNA causes FXTAS. The abnormal mRNA has been found in clumps of proteins and mRNA (intranuclear inclusions) that are found in brain and nerve cells in people with FXTAS. Some researchers speculate that the proteins found in the

inclusions cannot perform their normal functions, which could lead to the signs and symptoms of FXTAS. Another hypothesis is that the inclusions could cause the death of nerve cells important for movement and mental function. However, the exact role the inclusions play in the development of the disorder is unknown.

People with FXTAS may have a reduced amount of FMRP. While a reduction in this protein is not thought to be involved in FXTAS, it may lead to mild versions of features seen in fragile X syndrome (described above), such as prominent ears, anxiety, and mood swings.

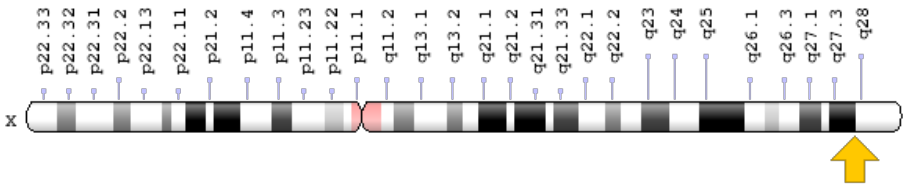
other disorders

Researchers have shown that some children with a premutation (55 to 200 CGG repeats) in the *FMR1* gene have learning disabilities, attention deficit hyperactivity disorder (ADHD), intellectual disability, or developmental disorders that affect communication and social interaction (such as autism spectrum disorders).

Chromosomal Location

Cytogenetic Location: Xq27.3, which is the long (q) arm of the X chromosome at position 27.3

Molecular Location: base pairs 147,911,951 to 147,951,127 on the X chromosome (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- FMR1_HUMAN
- FMRP
- FRAXA
- Protein FMR-1

Additional Information & Resources

Educational Resources

- National Fragile X Foundation: FMR1 Gene
  https://fragilex.org/fragile-x/genetics-and-inheritance/fmr1-gene/
- National Fragile X Foundation: FMRP – The Fragile X Protein
  https://fragilex.org/fragile-x/genetics-and-inheritance/fmr1-gene/fmrp-the-fragile-x-protein/
- National Fragile X Foundation: FXPOI
  https://fragilex.org/fragile-x/fxpoi/
- National Fragile X Foundation: FXTAS Information
  https://fragilex.org/fragile-x/fxtas/

GeneReviews

- FMR1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1384

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FMR1%5BTIAB%5D%29+OR+%28fragile+X+mental+retardation+1%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- FMR1 GENE
  http://omim.org/entry/309550

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_FMR1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=FMR1%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3775

- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2332
- UniProt
  http://www.uniprot.org/uniprot/Q06787

Sources for This Summary

- Bacalman S, Farzin F, Bourgeois JA, Cogswell J, Goodlin-Jones BL, Gane LW, Grigsby J, Leehey MA, Tassone F, Hagerman RJ. Psychiatric phenotype of the fragile X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. J Clin Psychiatry. 2006 Jan;67(1):87-94.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16426093
- Bretherick KL, Fluker MR, Robinson WP. FMR1 repeat sizes in the gray zone and high end of the normal range are associated with premature ovarian failure. Hum Genet. 2005 Aug;117(4):376-82. Epub 2005 Jun 2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16078053
- Galloway JN, Nelson DL. Evidence for RNA-mediated toxicity in the fragile X-associated tremor/ataxia syndrome. Future Neurol. 2009 Nov 1;4(6):785.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20161676
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821051/
- Garber K, Smith KT, Reines D, Warren ST. Transcription, translation and fragile X syndrome. Curr Opin Genet Dev. 2006 Jun;16(3):270-5. Epub 2006 May 2. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16647847
- GeneReview: FMR1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1384
- Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome--an older face of the fragile X gene. Nat Clin Pract Neurol. 2007 Feb;3(2):107-12.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17279084
- Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. Am J Hum Genet. 2004 May;74(5):805-16. Epub 2004 Mar 29. Review. Erratum in: Am J Hum Genet. 2004 Aug;75(2):352.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15052536
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1181976/
- Hagerman RJ, Leavitt BR, Farzin F, Jacquemont S, Greco CM, Brunberg JA, Tassone F, Hessl D, Harris SW, Zhang L, Jardini T, Gane LW, Ferranti J, Ruiz L, Leehey MA, Grigsby J, Hagerman PJ. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. Am J Hum Genet. 2004 May;74(5):1051-6. Epub 2004 Apr 2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15065016
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1181968/
- Hagerman RJ. Lessons from fragile X regarding neurobiology, autism, and neurodegeneration. J Dev Behav Pediatr. 2006 Feb;27(1):63-74. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16511373

- Hessl D, Wang JM, Schneider A, Koldewyn K, Le L, Iwahashi C, Cheung K, Tassone F, Hagerman PJ, Rivera SM. Decreased fragile X mental retardation protein expression underlies amygdala dysfunction in carriers of the fragile X premutation. Biol Psychiatry. 2011 Nov 1;70(9):859-65. doi: 10.1016/j.biopsych.2011.05.033. Epub 2011 Jul 23.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21783174
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191264/
- Hunsaker MR, Greco CM, Spath MA, Smits AP, Navarro CS, Tassone F, Kros JM, Severijnen LA, Berry-Kravis EM, Berman RF, Hagerman PJ, Willemsen R, Hagerman RJ, Hukema RK. Widespread non-central nervous system organ pathology in fragile X premutation carriers with fragile X-associated tremor/ataxia syndrome and CGG knock-in mice. Acta Neuropathol. 2011 Oct; 122(4):467-79. doi: 10.1007/s00401-011-0860-9. Epub 2011 Jul 23.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21785977
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222079/
- Jacquemont S, Hagerman RJ, Hagerman PJ, Leehey MA. Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMR1. Lancet Neurol. 2007 Jan;6(1):45-55.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17166801
- Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, Zhang L, Jardini T, Gane LW, Harris SW, Herman K, Grigsby J, Greco CM, Berry-Kravis E, Tassone F, Hagerman PJ. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. JAMA. 2004 Jan 28;291(4):460-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14747503
- Kenneson A, Zhang F, Hagedorn CH, Warren ST. Reduced FMRP and increased FMR1 transcription is proportionally associated with CGG repeat number in intermediate-length and premutation carriers. Hum Mol Genet. 2001 Jul 1;10(14):1449-54.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11448936
- Li Y, Jin P. RNA-mediated neurodegeneration in fragile X-associated tremor/ataxia syndrome. Brain Res. 2012 Jun 26;1462:112-7. doi: 10.1016/j.brainres.2012.02.057. Epub 2012 Mar 9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22459047
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3372578/
- Strom CM, Crossley B, Redman JB, Buller A, Quan F, Peng M, McGinnis M, Fenwick RG Jr, Sun W. Molecular testing for Fragile X Syndrome: lessons learned from 119,232 tests performed in a clinical laboratory. Genet Med. 2007 Jan;9(1):46-51.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17224689
- Tassone F, Beilina A, Carosi C, Albertosi S, Bagni C, Li L, Glover K, Bentley D, Hagerman PJ. Elevated FMR1 mRNA in premutation carriers is due to increased transcription. RNA. 2007 Apr; 13(4):555-62. Epub 2007 Feb 5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17283214
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1831862/
- Terracciano A, Chiurazzi P, Neri G. Fragile X syndrome. Am J Med Genet C Semin Med Genet. 2005 Aug 15;137C(1):32-7. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16010677

- Willemsen R, Mientjes E, Oostra BA. FXTAS: a progressive neurologic syndrome associated with Fragile X premutation. Curr Neurol Neurosci Rep. 2005 Sep;5(5):405-10. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16131424
- Wittenberger MD, Hagerman RJ, Sherman SL, McConkie-Rosell A, Welt CK, Rebar RW, Corrigan EC, Simpson JL, Nelson LM. The FMR1 premutation and reproduction. Fertil Steril. 2007 Mar;87(3): 456-65. Epub 2006 Oct 30. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17074338

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/FMR1

Reviewed: August 2012
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services